Prevalence of immune disease in patients with wounds presenting to a tertiary wound healing centre

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ABSTRACT

Chronic leg ulcers are a significant cause of morbidity and mortality and account for considerable healthcare and socioeconomic costs. Leg ulcers are a recognised complication of immune disease, and the purpose of this study was to establish the prevalence of immune disease in a cohort of patients with chronic wounds, and to compare wound outcomes in the subjects with and without immune disease.

Retrospective chart review was completed on consecutive patients scheduled with the plastic surgeon in the Georgetown University Center for Wound Healing between 1 January 2009 and 31 March 2009. Of the 520 patients scheduled for appointments, 340 were eligible for inclusion. The prevalence of immune disease was higher than expected with 78 of 340 patients (23%) having associated immune disease. At presentation, wounds in patients with immune disease had a significantly larger mean surface area [33·4 cm^2 (69·05) compared to 22·5 cm^2 (63·65), $P = 0·02$]. Split thickness skin graft (STSG) and bioengineered alternative tissue (BAT) graft data was available on 177 grafts from 55 subjects. There was a significantly lower response rate to STSG in subjects with immune disease (50% compared to 97%, $P = 0·0002$), but response rates to BAT were not different.

The association between immune diseases and chronic wounds may provide unique insights into pathways of wound healing, and warrants further study.

Key words: Bioengineered alternative tissue • Immune disease • Rheumatoid arthritis • Split thickness skin graft • Systemic lupus erythematosus

INTRODUCTION

Chronic leg ulcers are a significant cause of morbidity and mortality and account for considerable healthcare and socioeconomic costs. Studies show that the USA spends $25 billion per year on chronic wounds (1). Furthermore, a retrospective cohort study using data from the Centers for Medicare and Medicaid Services (CMS) found subjects with chronic wounds had a mortality of 28% over

Key Points

- in this cohort of patients evaluated by a plastic surgeon at a tertiary wound healing centre, the prevalence of immune disease was 23%
- the prevalence of rheumatoid arthritis, systemic lupus erythematosus, scleroderma, vasculitis, seronegative arthritis, inflammatory bowel disease, myasthenia gravis, multiple sclerosis and sarcoidosis was higher in this cohort than reported in the general population
- patients with immune disease had larger wounds at the initial visit than patients without immune disease
- patients with wounds and immune disease had significantly worse outcomes from split thickness skin grafts than patients without immune disease

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2 years of follow-up, compared to a mortality of 4% for the age-matched general population (2).

On a molecular level, wound healing is a highly regulated process which progresses through a series of overlapping phases including haemostasis, inflammation, proliferation and maturation regardless of the inciting aetiology of the wound (3). It is well recognised that some wounds are arrested in the inflammatory phase and are unable to progress to proliferation and maturation (3–6).

The prevalence of leg ulcers in the general population is approximately 1%. Autoimmune diseases are associated with a higher prevalence of leg ulcers, ranging from 4% to 9% depending on the disease and population studied (7–9). Only one prior publication has reported the prevalence of immune disease in patients with chronic ulcers. This study from a dermatology department evaluated 303 patients presenting to a multidisciplinary limb preservation clinic at the University of Pittsburgh over an 18-month period and identified 20 patients (6·6%) who had underlying collagen vascular disease or vasculitis (10). However, this data is limited because it is only reported in conjunction with a review article and further information on the cohort studied is not available. As tertiary wound healing centres are increasingly utilised to optimise management of patients with complex, refractory and recalcitrant wounds (11), it is important that the prevalence of immune disease in this population is recognised.

Treatment of patients with recalcitrant wounds is extremely challenging (4,12). Surgical therapies for wounds include split thickness skin grafts (STSG) which are used to achieve definitive tissue and wound closure and grafts using bioengineered alternative tissues (BAT) that are used to achieve wound coverage while waiting for optimisation of the wound bed. Several BAT products are available and their individual characteristics are well reviewed elsewhere (13). Xenograft is a porcine-derived dermis and epidermis which is irradiated to remove the cellular component. Human-derived skin equivalents generally include a collagen and dermal matrix with live allogenic human keratinocytes and fibroblasts derived from human foreskin. Examples include AlloDerm® Integra™ and Dermagraft™, and these agents have been used successfully for treating burn wounds (14, 15). The composite skin equivalent Apligraf® is also frequently used in clinical practice and consists of epidermal and dermal elements with bovine collagen, allogenic fibroblasts and epidermal cells. It has been shown to be beneficial in preparation of a wound bed for STSG in venous stasis ulcers when combined with compression, and in healing of diabetic ulcers (13). Use of Apligraf® has been extrapolated on a case-by-case to other chronic refractory ulcers such as those seen in vasculitis and systemic and localised scleroderma (13,16), but it has not been studied specifically for use in patients with immune-mediated ulcers.

The primary purpose of this study was to establish the prevalence of immune disease in a cohort of patients with chronic wounds presenting to a university-based tertiary wound healing centre in the USA. Secondarily, using this retrospective cohort we wished to compare wound outcomes, including healing rates, and outcomes from STSG and BAT (in our clinic Apligraf®, xenograft and Dermagraft™) in the subjects with immune disease to those without immune disease.

METHODS

This study protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki and was approved by the Biomedical Institutional Review Board of Georgetown University.

Study population

The Center for Wound Healing at Georgetown University Hospital is a tertiary limb-salvage and wound healing centre. At the time that this study was conducted, the centre had one full time plastic surgeon and one full time podiatric surgeon. Retrospective chart review was completed on consecutive patients scheduled with the plastic surgeon between 1 January 2009 and 31 March 2009 (index visit). Data collection was completed between 1 August 2010 and 30 October 2010.

Inclusion and exclusion criteria

Patients who did not attend the appointment, those without an open wound, and those who were only scheduled with podiatry were excluded. It should be noted that in our centre patients with complex foot wounds are

typically evaluated by both the plastic surgeon and the podiatrist, so this selection criteria ensured inclusion of most patients with refractory wounds while excluding subjects with purely biomechanical foot issues.

Data collection

Data were abstracted from the Centricity electronic medical record version 9.0 (General Electric Medical Systems, GE Healthcare, UK). Patient demographics and comorbidities including presence of diabetes, venous and arterial disease, and autoimmune diseases were recorded. Wound-specific data including wound duration, size of the wound at first visit, and total duration of follow-up with wound outcome was recorded based on review of the electronic medical record including chart data available from visits prior to and since the index visit. We designed the study so that chart review was completed 16–19 months after the index visit, so that where possible approximately 1 year of follow-up data was available.

Assessment of comorbid conditions

This was a retrospective study and presence of comorbid conditions was ascertained by review of the medical record. ICD-9 codes were used to identify comorbidities, and the clinical chart was reviewed to confirm that the subject met criteria for the diagnosis in question.

Patient and physician records were used to confirm presence or absence of diabetes. Clinical and diagnostic evaluations were used to confirm presence or absence of venous and arterial disease.

To confirm a diagnosis of immune disease, chart documentation of subspecialty evaluation was reviewed by a rheumatologist (VKS) to ensure that the subject met diagnostic criteria for the disease in question. American College of Rheumatology (ACR) criteria were used to confirm the diagnosis of rheumatoid arthritis (17), systemic lupus erythematosis and mixed connective tissue disease (18), Sjogren's syndrome (19), and vasculitis (20,21). Diagnosis of seronegative arthritis and sarcoidosis was based on clinical manifestations. LeRoy and Medsger criteria (22) were used to confirm diagnosis of scleroderma and to classify disease subtype. For the diagnosis of antiphospholipid syndrome subjects had to fulfil the revised Sapporo Criteria (23). For the diagnosis of multiple sclerosis and myasthenia gravis, subjects had to be followed by neurology with documentation of a confirmed diagnosis in the patient chart.

Atrophie Blanche is a clinicopathologic diagnosis based on clinical presentation of a wound that heals with stellate porcelain white scarring and that exhibit pathologic features of a fibrin occlusive vasculopathy (24–28). This entity has been reported in association with numerous immune diseases (24,29–32), and has also been seen in association with prothrombotic states (25). For the purposes of this study, charts from subjects with reported atrophie blanche were reviewed for immune and prothrombotic work-up and any biopsy specimens were reviewed to confirm presence of fibrin occlusive vasculopathy. If chart review identified associated immune disease then the subject was classified as having that immune disease, in contrast, subjects with no other aetiology and those who had not undergone full immune work-up were classified as having isolated atrophie blanche.

Data on immune disease prevalence

To obtain an estimate of immune disease prevalence in the general population a comprehensive literature search of PubMed was performed for each immune disease, and prevalence of the disease in question in the US population was used as the reference prevalence. When prevalence data based on a US population was not available, the closest available approximation to a US population was used as the reference prevalence.

Local wound care and surgical procedures

Local wound care and surgical grafting procedures were performed according to standard protocols under the direction of the plastic surgeon. Billing and coding records were used to identify patients who had undergone graft procedures. Patients undergoing surgery in our centre are routinely seen pre-operatively for wound measurements (pre-op visit), for a post-operative visit at 10–14 days and for a graft assessment visit at 28–32 days (30-day visit). The electronic medical record was used to abstract data on wound measurements from the pre-op and the 30-day visits. The wound measurements were used to calculate percentage change in wound size, and this was then

stratified into response (>50% reduction in wound surface area) and no response (<50% reduction in wound surface area). In analysis of the graft data, only grafts with sufficient data in the record to assess graft outcome were included in the analysis. Patients undergoing skin flaps and other reconstruction surgeries for wound closure were not included in this analysis. Data was analysed by graft type (Apligraf®, Dermagraft™, xenograft or STSG).

Biopsy data

Biopsy reports were reviewed for all biopsy samples and presence or absence of vasculitis, thrombosis and granuloma formation was documented, along with any other diagnostic features.

Statistical analysis

For continuous variables data was analysed using Wilcoxon Rank-Sum test and for categorical variables Chi-square test was used. For comparison of prevalence rates, *P*-values were computed using the one-sample proportion test procedure using Stata version 11.0 (Stata Corp, College Station, TX). For all analyses a *P*-value $< 0{\cdot}05$ was considered statistically significant. Data is given as mean and standard error of the mean (SEM) when normally distributed.

RESULTS

Of the 520 patients scheduled for appointments in the study period, 340 were eligible for inclusion with an open ulcer at the time of evaluation. The remaining 180 patients either did not attend the visit, or did not have an ulcer at the time of the visit (Figure 1).

Prevalence of immune diseases and other comorbidities

Prevalence of diabetes, venous and arterial disease in this cohort was similar to that expected, with diabetes present in 168 patients (49%), venous disease in 120 (35%) and arterial disease in 118 (35%, Figure 1A), with some overlap between these comorbidities (Figure 1B). However, the prevalence of immune disease was higher than expected with 78 of 340 patients having associated immune disease, giving an overall prevalence of immune disease in this cohort of 23%. The breakdown of associated immune diseases is shown in Figure 1C.

Biopsy data

Biopsy data was available for 57 of the 79 subjects with associated immune disease. Of these, 12 patients had biopsy proven evidence of vasculitis, 8 samples were gangrenous, 7 had evidence of thrombosis and 30 had non specific granulation tissue with acute and chronic inflammation. These findings are consistent with prior case series reporting biopsy findings in subjects with known autoimmune disease such as rheumatoid arthritis, in which leukocytoclastic vasculitis is not always seen on biopsy (33,34) and non specific findings are often seen.

Comparison with prevalence of immune disease in the general population

Table 1 shows the prevalence of each associated immune disease in our cohort compared to disease prevalence in the general population and demonstrates that the prevalence of immune diseases in patients with leg ulcers was significantly higher than expected based on reported prevalence rates from the literature for all diseases except for primary Sjogren's syndrome.

Features and outcomes of immune-mediated wounds

Immune diseases were more common in women, likely reflecting the well-established preponderance of immune diseases, particularly rheumatoid arthritis, systemic lupus erythematosis and scleroderma, in women (Table 2). Subjects with immune disease had significantly larger wounds [mean $33{\cdot}4\ cm^2$ (SD $69{\cdot}05$) compared to $22{\cdot}5$ ($63{\cdot}65$), $P = 0{\cdot}02$] at the first visit. Pain scores tended to be higher in the subjects with immune disease but this did not reach statistical significance. While there was no significant difference in percentage of wounds that healed in the follow-up period, time to healing was more prolonged in subjects with immune diseases (mean $10{\cdot}3$ months compared to $14{\cdot}6$ months, $P = 0{\cdot}07$).

Graft outcomes

Response to STSG and BAT data was available on 177 grafts from 55 subjects. Outcome was categorised into response (>50% reduction in wound surface area at 30 days) or no response (<50% reduction in wound surface area at 30 days, Table 3). Combining all graft

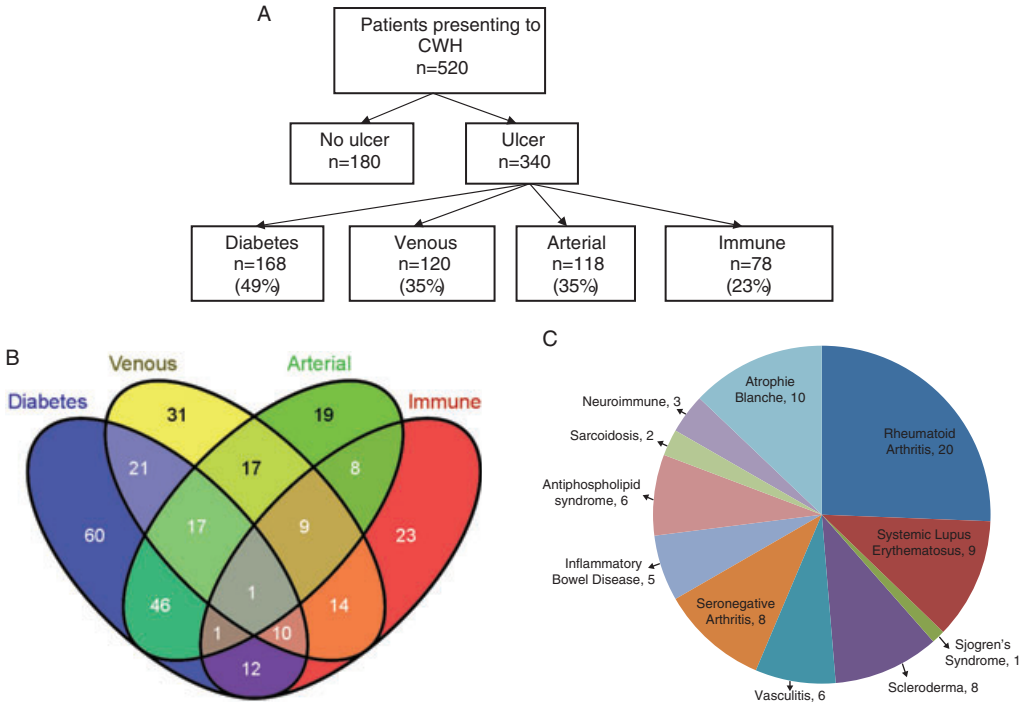

Figure 1. (A) Flowchart showing prevalence of diabetes, venous, arterial and autoimmune disease in a retrospective cohort of 340 patients with recalcitrant wounds. (B) Venn diagram showing overlap of diabetes, venous and arterial disease with immune disease. The overall prevalence of immune disease was 23% which was higher than expected. (C) Pie chart showing associated immune diseases and number of patients with each disease.

types (STSG and BAT), the response rate in subjects with immune disease was lower (33% compared to 47%) but this did not reach statistical significance ($P = 0{\cdot}08$). When the outcome was broken down by graft type, there was no significant difference in outcome of Xenograft, Dermagraft™ or Apligraf® in subjects with immune disease compared to those without. However, there was a significantly lower response rate to STSG in subjects with immune disease (50% response compared to 97% response, $P = 0{\cdot}0002$).

DISCUSSION

Although chronic wounds and lower extremity ulcers are a known complication of autoimmune diseases (7,9,29), the prevalence of immune diseases in patients presenting with chronic wounds has previously been reported to be 6·6% (10). We found a much higher prevalence of immune diseases (23%) in this population of patients evaluated by a plastic surgeon in a specialised wound healing centre. As patients in our centre tend to have more recalcitrant wounds than those seen in primary care and smaller wound healing centres, selection bias may have contributed to the higher than expected prevalence in this cohort. However, it should be noted that our study relied on data abstracted from the medical record, a methodology that might underrepresent immune diseases by introducing reporting and documentation bias. For comorbidities that are aggressively screened for and documented in our routine clinical management of patients, such as diabetes, venous and arterial disease, any reporting bias is likely to be minimal. For the immune diseases however, the impact of reporting bias may have underestimated the prevalence of these diseases. In prevalence studies of rheumatoid arthritis, 'self-reported doctor-diagnosed arthritis' is used to estimate arthritis prevalence and this has been demonstrated to be a rigorous methodology with acceptable sensitivity and specificity (35). Our methodology was even more stringent, in that charts that were identified with a diagnosis of rheumatic or immune disease were re-reviewed by a rheumatologist to confirm there was sufficient documentation in the form of consultant reports to support

Table 1 Prevalence of immune diseases in this cohort of 340 patients with open ulcers evaluated at the Georgetown University Hospital Center for Wound Healing

	n/340	Prevalence in the literature (%)	Prevalence in this cohort (%)	*P* value	References
Rheumatoid arthritis	20	0·6–1	5·9	**<0·001**	(35,36)
Systemic Lupus Erythematosus (SLE)/ Mixed Connective Tissue Disease (MCTD)	9	0·05–0·15	2·6	**<0·001**	(37,38)
Sjogren's Syndrome	1	0·6	0·3	0·47	(35)
Scleroderma	8	0·02	2·35	**<0·001**	(35,39)
Vasculitis	6	0·278 (GCA) 0·739 (PMR) 0·002 (ANCA assoc. vasculitis)	1·8	**0·027**	(40,41)
Seronegative arthritis	8	0·1–0·2	2·35	**<0·001**	(35,42,43)
Inflammatory bowel disease	5	0·44	1·5	**0·004**	(44)
Antiphospholipid syndrome	6	No data	1·8		
Sarcoidosis	2	0·04	0·6	**<0·001**	(45)
Neuroimmune	3	MG: 0·02 MS: 0·09	0·9	**<0·001**	(46–48)

Prevalence in the study cohort was compared to prevalence for each disease as reported in the literature for the general population. *P* values were computed using the one-sample proportion test. *P* value of $< 0{\cdot}05$ was considered significant. Neuroimmune wounds included subjects with myasthenia gravis (MG) and multiple sclerosis (MS). Vasculitic wounds included subjects with polymyalgia rheumatica (PMR), giant cell arteritis (GCA), Buerger's disease, Takayasu's arteritis and anti-neutrophil cytoplasmic antibody (ANCA) associated vasculitis. Since the prevalence of all of these diseases is low, the pooled prevalence was used for the comparison in the one-sample proportion test.

the diagnosis. These rigorous criteria may actually have led to an under-estimation of disease prevalence in our cohort. Our observation underscores the importance of considering associated immune disease in subjects with recalcitrant wounds. Further studies to investigate the association between immune diseases and chronic wounds in larger and more generalisable populations is warranted.

The overlap of comorbidities seen in our population (Figure 1B) was consistent with that of other authors suggesting that many subjects with immune disease may have co-existent venous or arterial disease (49) and reiterating the importance of continuing to manage these patients in multidisciplinary wound healing centres where comorbidities can be appropriately screened for and treated.

Studies reporting utility of BAT and STSG in patients with immune disease are restricted to case series and case reports describing off-label use (13,16,50, 51). Our analysis of graft outcome data found that subjects with immune disease had significantly worse outcomes with STSG compared to subjects without immune disease. In contrast the BAT outcomes did not differ between the two groups, suggesting that as with chronic wounds from other aetiologies, BAT remains a temporising option for these patients while medical evaluation and therapy is ongoing. There were several limitations of the graft outcome data reported here that merit further discussion. Firstly, the time of the study was selected to coincide with introduction of our electronic medical record, since this facilitated data retrieval. However, as is often a problem with retrospective data retrieval, graft outcome data was incomplete in some subjects so analysis was restricted to grafts with sufficient outcome data. Secondly, an inherent bias related to the retrospective methodology was that grafts were performed as dictated by the clinical status of the wound, with the selection of subjects for grafting, and graft tissue selection determined by the wound healing team. While this may have introduced selection bias both in regards fewer immune subjects undergoing grafting, and fewer patients with immune diseases undergoing STSG we were still able to demonstrate a significantly lower response rate to STSG in subjects with immune disease compared to those without (50% compared to 97%, $P = 0{\cdot}0002$). This observation is important not only for the clinical management

Table 2 Demographic features of subjects, stratified by presence or absence of immune disease

	No immune disease $n = 262$	Immune disease $n = 78$	*P* value
Age, years			
Mean (SD)	63·89 (16·5)	67·77 (16·7)	0·08
Median (range)	64·5 (11–100)	72·0 (33–94)	
Race			
Caucasian	136 (52%)	40 (51%)	0·92
African American	106 (40%)	32 (41%)	0·92
Hispanic	6 (2·3%)	2 (2·6%)	0·88
Other	14 (5·3%)	4 (5·1%)	0·94
Sex			
Male	143 (55%)	25 (32%)	**0·0005**
Female	119 (45%)	53 (68%)	
Wound size, cm^2			
Mean (SD)	22·5 (63·65)	33·4 (69·05)	**0·02**
Median (range)	3·0 (0·03–780)	6·9 (0·04–432)	
Pain score			
Mean (SD)	2·48 (3·29)	3·32 (3·67)	0·08
Median (Range)	0 (0–10)	2 (0–10)	
Wound healed at final follow-up, *n* (%)	107 (41%)	31 (40%)	0·90
Total follow-up, months			
Mean (SD)	10·3 (7·49)	14·2 (11·01)	**0·0025**
Median (range)	10 (0–31)	13·5 (0–76)	
Time to healing, months			
Mean (SD)	10·3 (7·01)	14·6 (13·1)	**0·07**
Median (range)	10·25 (0·5–28·8)	12·2 (0·9–75·6)	

P values were computed using Wilcoxon Rank-Sum test for continuous variables, and Chi-square test for categorical variables. A *P* value of $< 0·05$ was considered significant.

Table 3 Outcome of Apligraf®, Dermagraft™, xenograft and split thickness autologous skin graft (STSG) stratified by presence or absence of immune disease

	No immune disease	Immune disease	*P* value
Apligraf® ($n = 90$)	19/63 (30%)	10/27 (37%)	0·52
Dermagraft™ ($n = 3$)	1/3 (33%)	0/0	not reported
Xenograft ($n = 42$)	9/30 (30%)	1/12 (8%)	0·14
Split thickness skin graft ($n = 42$)	31/32 (97%)	5/10 (50%)	**0·0002**
All graft types ($n = 177$)	60/128 (47%)	16/49 (33%)	0·08

Numbers are listed as number of responders/number of grafts performed (%) in each category. *P* values were computed using the chi-square test. *P* value of $< 0·05$ was considered significant.

of wounds in patients with known immune disease, but leads us to speculate that graft failure may be a predictor of underlying immune disease and that subjects who fail a STSG warrant immune evaluation.

While the observed associations do not demonstrate causality, further study of the associations between immune diseases and delayed wound healing could yield insights into mechanisms by which inflammatory pathways impact angiogenesis and new tissue formation. Many questions remain regarding the best clinical management of patients with immune disease and chronic wounds. Historically clinicians have been cautious about using systemic immunosuppressive therapy in patients with open wounds. However, data from our small cohort of patients with rheumatoid arthritis-associated ulcers (9) suggests that aggressive therapy for the underlying immune disease, in the case of rheumatoid arthritis with targeted anti-tumor necrosis factor biologic therapy, results in better wound outcomes.

A prospective observational study, the Wound Etiology and Healing Study (WE-HEAL Study, ClinicalTrials.gov NCT01352078) is currently underway at Georgetown University Hospital and will permit correlation of clinical, serologic, pathologic and epidemiologic features and to study the impact of immune and other diseases along with therapeutic interventions on wound outcomes.

CONCLUSION

The prevalence of immune-mediated wounds in this consecutive cohort of patients with wounds presenting to a tertiary wound healing centre was 23% which is higher than previously reported. The prevalence of rheumatoid arthritis, systemic lupus erythematosus, scleroderma, vasculitis, seronegative arthritis, inflammatory bowel disease, myasthenia gravis, multiple sclerosis and sarcoidosis was higher in this cohort than reported in the general population. Wounds in patients with immune disease were larger at presentation, and subjects with immune disease had significantly worse outcomes in response to STSG compared to those without immune

disease. Response rates to BAT were not significantly different between the two groups. As a result of our observations, we suspect the association between immune diseases and chronic wounds has the potential to yield new insights into mechanisms of delayed healing. Further studies of the population of patients with recalcitrant wounds and immune disease are warranted.

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